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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/238,741	01/28/1999	GARY R. BRASLAWSKY	012712-584	5956

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/238,741	BRASLAWSKY ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *3,10-13,15-23,30-33,38-40 and 42-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,14,24-29,34-37,41 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

Attachments

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4. ☐ Interview Summary (PTO-413) Paper No(s). _____
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Other

DETAILED ACTION

Request for Continued Examination

1. The request filed on 6/3/02 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/238,741 is acceptable and a RCE has been established. Claims 1-49 are pending and claims 1, 2, 4-9, 14, 24-29, 34-37, 41, 45-49 are currently under prosecution. An action on the RCE follows.

2. Claims 1-49 are pending.

Claims 1, 24, and 37 have been amended.

3. Claims 3, 10-13, 15-23, 30-33, 38-40, 42-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made without traverse in Paper No 4.

4. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 45-49 are under examination.

5. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

6. The following contains some NEW GROUNDS of rejection.

Oath/Declaration

7. The Examiner acknowledges that a new Declaration will be submitted in due course as indicated in the amendment filed 4/11/02, however, the oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The name of the inventor Michael V. LaBarre has been altered to replace the "V" with a "J". In addition the name "Garry R. Braslawsky has been altered to "Gary Ronald Braslawsky"

Rejections Withdrawn

8. The rejection of claims 1-2, 4, 5-9, 24-29, 34, 36, 37 and newly submitted claims 47-49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims and reconsideration.

9. The rejection of claims 2, 4, 28, 41, and 46 under 35 U.S.C. 102(b) as being anticipated by Brennen et al (Science 229:81-83, 1985) is withdrawn.

10. The rejection of claims 1-2, 4-9, 14, 24-29, 34-37, 41, 45-49 under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention is withdrawn in view of arguments.

11. The rejection of claims 1-2, 4-9, 14, 24-29, 34-36, 41, 47-49 under 35 U.S.C. 103(a) as being unpatentable over Caron et al (J. Exp. Med. 176:1191-1195, 1992) and further in view of Fanger et al (Critical Reviews in Immunology 12:101-124, 1992) and Cumber et al (J. Of Immunol. 149:120-126, 1992) and Reff et al [a] (U.S. Patent 6,011,138, filed 2/20/97) and Reff et al [b] (Blood 83:435-445, 1994) is withdrawn in view of the amendments to the claims

Response to Arguments

12. The rejection of claims 45 and 46 under 35 U.S.C. 112, first paragraph, is maintained.

The response filed 4/11/02 has been carefully considured but is deemed not to be persuasive. The response states that the claims have now been revised to recite an antibody heterodimer composed of two different antibody molecules and wherein the cysteine location does not interfere with antigen binding (see pages 6-7 of response). In response to these arguments, claim 45 does not recite such limitations and encompasses a cysteine residue any where in the molecule.

13. The rejection of claim 35 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained.

The response filed 4/11/02 has been carefully considered but is deemed not to be persuasive. The response did not address this rejection directly but does mention that patent 5,830,698 and 6,011,138 both provide extensive discussion of the C2B8 and p5E8 antibodies (see page 5 of response of 4/11/02). In response to this argument, it is still not clear if the hybridomas that produce the antibodies are commercially available. The claims require the entire antibodies and the specification teaches combining the molecules but the molecules themselves are required for the practice of the invention

14. The rejection of claims 37, 45-46 under 35 U.S.C. 103(a) as being unpatentable over Caron et al (J. Exp. Med. 176:1191-1195, 1992) and further in view of Fanger et al (Critical Reviews in Immunology 12:101-124, 1992) and Cumber et al (J. Of Immunol. 149:120-126, 1992) and Reff et al [a] (U.S. Patent 6,011,138, filed 2/20/97) and Reff et al [b] (Blood 83:435-445, 1994) is maintained.

The response filed 4/11/02 and 6/3/02 has been carefully considered but is deemed not to be persuasive. The response of 4/11/02 argues that the references fail to teach two different antibody molecules having distinct antigen binding specificities (see page 11 of response) and the response filed 6/3/02 argues that the present invention is of two intact antibody molecules not half-antibody molecules (see page 1 of response). In response to arguments the art of Caron teaches a dimeric antibody and the art of Fanger teaches a dimeric antibody with two specificities (see Figure 1 of both references. The rejected claims only require a dimeric antibody with two specificities or a heterodimeric antibody. Thus the references reads on the claims.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

15. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are indefinite for reciting

and 37(iv) because the exact meaning of the phrase is unclear. It is unclear if the

procedure is to reduce all disulfide bonds such as those in the hinge region or is the procedure to only reduce the cysteine that was engineered into the heavy chain?

b. Claims 1-2, 4-9, 14, 47-48 are indefinite for reciting part (v) in claim 1 because the exact meaning of the phrase is not clear. Part (v) is not clear because it is not clear how contacting the reduced antibody in step (Iv) with the antibody in step (V) produces the heterodimer. The antibody in step (V) is not reduced or does not contain any thiol reactive groups to form a heterodimer.

c. Claim 37 is indefinite for reciting part (iv) because the exact meaning of the phase is unclear. It is unclear how a heterodimer which binds two distinct antigens can be produced when only one antibody with one specificity is used for the making the dimer.

d. Claims 28 and 41 are indefinite for depending on non-elected claims.

e. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are indefinite for reciting "an antibody molecule heavy chain that has binding specificity" in claims 1, 24, and 37 because the exact meaning of the phrase is not clear. Does the phrase mean the heavy chain binds antigen or does the phrase mean that the heavy chain when paired with a corresponding light chain binds antigen?

16. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of

introducing a cysteine residue by recombinant mutagenesis into the heavy chain wherein the location of the introduced cysteine residue when paired with a light chain does not interfere with antigen binding of the heterodimer and expressing the heavy and light chains and reducing the cysteine residue introduced such that when contacted with another antibody that contains a thiol reactive group and does not have a cysteine residue introduced and allowing sufficient time for the two antibody molecules to form a heterodimer thought the thiol reactive group and the introduced cysteine and the antibody heterodimer produced by such method, does not reasonably provide enablement for a method for producing an antibody heterodimer wherein the antibody which has a cysteine residue introduced is reduced and contacted with an antibody that does not have a cysteine introduced or contacting the reduced antibody with a crosslinking reagent of bis-maleimido to produce the heterodimer and the antibody produced by such methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

The claims are broadly drawn to a method of producing an antibody heterodimer by introducing a cysteine residue into a heavy chain and expressing the heavy and light chain and reducing all disulfide bonds in the antibody and contacting the reduced antibody with another antibody that is not reduced (claim 1) or producing an antibody that is dimerized through any of the cysteine residues not just the cysteine residue introduced by recombinant mutagenesis (claim 24) or producing an antibody heterodimer by contacting the reduced antibody with a cross-linker of Bis-maleimido (claim 37 which does not require an additional antibody of another specificity). The claims broadly encompass method that do not produce a heterodimer of two antibody molecules wherein each antibody binds a different antigen or where the antibodies are conjugated by the cysteine residue engineered into the antibody heavy chain. The specification teaches the production of an antibody heterodimer wherein the heterodimer binds two antigens and the antibodies are conjugated through a cysteine residue introduced into one of the antibodies heavy chain and through a bis-maleimido crosslinker to the other antibody which does not contain a cysteine introduced therein (see examples and Figure 4). The specification does not teach an antibody heterodimer wherein each antibody molecule of the heterodimer binds a different antigen when the antibodies are produced by reducing all disulfide bonds in the antibody molecule and adding either any antibody that is not reduced or adding only a crosslinker or reducing all disulfide bonds in the antibody and adding an antibody that contains a thiol reactive

By the specifications definition an antibody heterodimer is a molecule that comprises two antibody molecules that bind two different antigens (see page 1, lines 7-9). The claims encompass adding a reducing agent to reduced the intra and inter disulfide bonds of an antibody. As evidenced by Cruse et al (Illustrated Dictionary of Immunology, CRC Press, page 19, 1995) an antibody molecule is made up of several disulfide bonds such as those in the hinge region, and between the light and heavy chains therefore partially reducing the molecule would produce a combination of molecules which are not intact antibody molecules comprising the entire VL, VH, CH1, CH2, CH3 as required by an intact whole antibody. One skill in the art would not expect an antibody that was reduced in the hinge or between the heavy and light chains when combined with either an other antibody that is not reduced as required in claim 1 or a molecule that contained a thiol reactive group (as required by claim 24) or only adding a crosslinker with no additional antibody (as required by claim 37) would produce the desired heterodimeric antibody. The claims encompass a myriad of molecules that are reduced or partially reduced that when combined with another antibody would not produce the claimed product of a heterodimer.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

17. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caron et al (J. Exp. Med. 176:1191-1195, 1992, PTO-892) and further in view of Fanger et al (Critical Reviews in Immunology 12:101-124, 1992, PTO-892) and Cumber et al (J. Of Immunol. 149:120-126, 1992, PTO-982) and Reff et al [a] (U.S. Patent 6,011,138, filed 2/20/97, PTO-892) and Reff et al [b] (Blood 83:435-445, 1994, PTO-892) and The Pierce Catalog (pages T-157, T-163-169, 1994-95).

The claims recite a method for producing an antibody heterodimer composed of two different antibody molecules having binding specificities to two distinct antigens comprising obtaining or constructing a DNA molecule that encodes a heavy chain and introducing at least one cysteine codon and expressing the DNA with DNA encoding a light chain and purifying the antibody and contacting the antibody with a reducing agent to reduce the intra or inter molecular disulfide bonds and either allowing for dimerization or adding an antibody that contains a thiol reactive group, or adding a BIS-maleimido crosslinker. Further claimed is an heterodimer, which is capable of activating components of the complement system and which kills cells and binds Fcgamma on effector cells and on immune cells and is capable of initiating apoptosis wherein the dimer is reactive against CD20 and CD23 and wherein the IgG's are of the same or different subclass and different isotypes and bind two different epitopes and is C2B8/p5E8 and compositions comprising such.

Caron et al teach a method for producing a dimeric IgG which comprises

Ellman's reagent and allowing dimerization. (See Materials and methods). The antibody has enhanced CMC and ADCC with human effector cells (see introduction page 1191). Caron et al does not teach a heterodimer, adding a thiol reactive group introduced on another antibody, an anti-CD23 antibody or an anti CD20 antibody. These deficiencies are made up in the teachings of Fanger et al, Cumber et al, Reff et al [a] and [b] and the Piece Catalog.

Fanger et al teach bispecific antibodies by chemical cross linking or by molecular genetic approaches (see page 102, section II and Figure 1).

Cumber et al teach a bispecific antibody produced by chemical cross linking with a maleimido group with the cysteine residues (see Figure 2) wherein one is introduced in the heavy chain (see page 22, Results).

Reff et al [a] teach the anti-CD23 antibody (p5E8) and Reff et al [b] teach the anti-CD20 antibody (C2B8).

The Pierce Catalog teaches heterobifunctional crosslinkers for conjugation with specific groups to minimize undesirable polymerization or self-conjugation. The cross-linkers are amine and sulfhydryl-reactive.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens.

heterodimeric antibody molecule comprising two different antibodies which bind two antigens because Caron et al teach "Several lines of evidence suggest that the proximity of Fc regions of multimeric IgG may explain its enhanced effectiveness in CMC as compared to monomeric IgG." (See page 1194) and "multimeric constructs of IgG may have advantages relative to those forms that are found naturally." (See abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens because Fanger et al teach "Chemical linkage is the most straightforward procedure for making a pure BsAb;" (see page 102) and "BsAb can bind both to target cells (pathogens and tumors) and to toxins, enzymes, or triggering molecules on leukocytes such as T-cell receptors (TcR) or Fc R." (See page 102). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens because Cumber et al teach that "the sulfydryl group so introduced served as a specific site for the attachment of the homobifunctional cross-linking reagent" (see page 122). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens because Reff et al [a] teach

the subject antiCD23 antibody are effective in treating any disease wherein inhibition of IgE production is therapeutically desirable" (column 38, lines 42-46) and Reff et al [b] teach CD20 is on the surface of B-cell lymphomas and C2B8 showed ability to bind to human C1q, mediate complement-dependent cell lysis of human B-lymphoid cells. In addition, one of ordinary skill in the art would be motivated to and had a reasonable expectation of success to have produced a method for producing a heterodimeric antibody molecule comprising two different antibodies which bind two antigens because The Pierce Catalog teaches heterobifunctional crosslinkers for conjugation of proteins and the heterobifunctional crosslinkers have the advantage of minimizing undesirable polymerization or self-conjugation which would result in a higher purity of the heterodimeric product and not the undesirable product of a homodimer. In addition, one skilled in the art would want to produce a heterodimeric anti-CD20 and CD23 antibody because one skilled in the art would know that targeting the CD23 would result in lower levels of IgE and targeting the CD20 with C2B8 would result in the lysis of the B-cell.

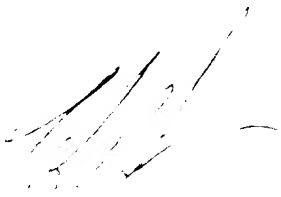
Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,



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